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CHARACTERIZATION AND STABILITY OF CYCLIC DISULFIDES AND CYCLIC DIMERIC BIS(DISULFIDES)

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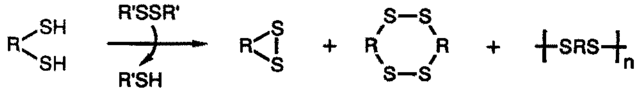
Abstract. This paper describes the preparation of cyclic bis(disulfide) dimers derived from trans-2-butene-1,4-dithiol and cis-1,2-cyclohexane dithiol and the cyclic tris(disulfide) dimer of 1,3,5-tris(mercaptomethyl)benzene by high dilution oxidation of the thiols with iodine. The stability toward ring-opening polymerization of these three new cyclic disulfides and of nine previously reported cyclic disulfides was tested by heating the disulfide with a catalytic amount of sodium methanethiolate. None of the cyclic bis(disulfides) were stable with respect to polymerization under these conditions. The results of these experiments, together with literature reports concerning the stability of similar disulfides, indicate that few simple alkyl disulfides are thermodynamically stable in cyclic form.

Introduction

As part of a study of the relation between structure and properties of the disulfides formed by oxidation of thiols using thiol-disulfide interchange reactions,[1-3] we have been interested in the distribution of products obtained from organic dithiols among monomeric disulfides, cyclic bis(disulfides), and oligomeric and high molecular weight disulfide-containing species (eq 1). The question of central mechanistic interest in



(1)

this work concerns the factors required to favor formation of the cyclic bis(disulfide): in particular, what structures for the group R favor bis(disulfide) at thermodynamic equilibrium? Although it is straightforward to specify structural classes that generate monomeric disulfides or polymeric disulfides on oxidation, identifying the structural features required to favor cyclic bis(disulfides) has proved to be difficult. The major problem seems to be a consistently unfavorable enthalpy of formation of the cyclic bis(disulfide) relative to polymer, probably originating in CSSC angle strain.

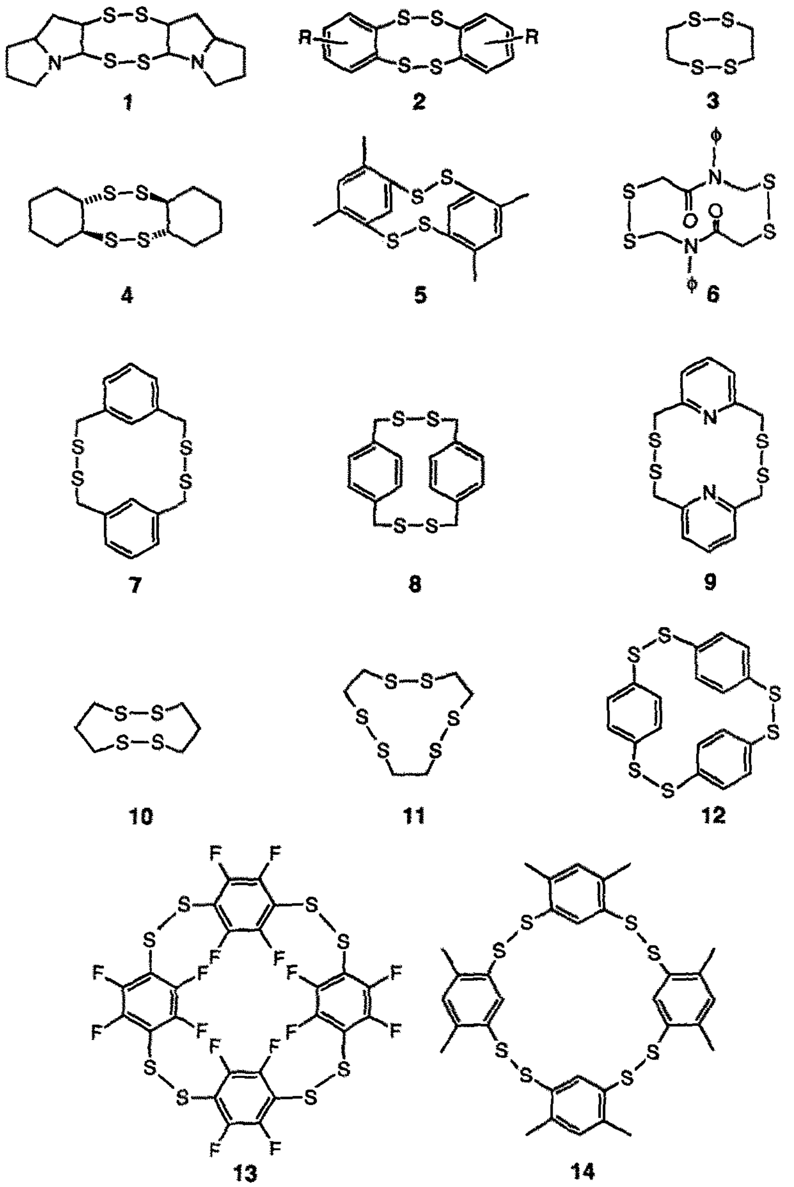
We and others have reported the formation of cyclic bis(disulfides) and related discrete tris- and tetrakis(disulfides) under a number of conditions, but the question of whether these substances represent kinetic or thermodynamic products has not been systematically addressed. This paper describes the preparation of several cyclic bis- and tris(disulfides) under kinetic conditions, and establishes that these compounds are unstable with respect to polymer in concentrated systems. The paper also collects and reviews the literature relevant to this subject. This information is useful in three ways. First, it establishes the relative stability of the cyclic bis- and tris(disulfides) and their derived polymeric disulfide forms. Second, examination of the spectral properties of the pure bis(disulfides) is helpful in verifying whether these compounds are formed, even at low concentrations, under equilibrating conditions. This information is especially helpful in studies of weakly reducing dithiols; it is often difficult to distinguish unambiguously between formation of linear oligomeric disulfides and formation of cyclic dimeric products. Third, the ease with which the low molecular weight cyclic disulfide-containing species convert to polymers makes cyclic bis(disulfides) potentially useful in polymer science: High molecular weight polysulfide polymers have been obtained from the oxidation of α,ω-dithiols[4] and from the self-polymerization of cyclic disulfides.[5] Thiols and disulfides are also important cross-linking reagents in polymers.[6,7] The ease with which disulfide bonds can be reduced to thiols also makes reversible polymer formation possible.[8]

A number of cyclic bis(disulfides) and higher cyclic disulfides are reported in the literature: Compounds **1-14** provide examples (Figure 1). Crystal structures are available for compounds 1,[9] 3,[10] 7,[11] 8,[12] 10,[10] 11,[10] and 14.[16]

A variety of substituted dibenzo[1,2,5,6]tetrathiocins, 2, have been reported.[13,14] The parent compound is a yellow solid with an ill-defined melting range.[13] Tetrathiocin **4** has been described as a stable colorless solid with a sharp melting point.[15] Compounds **3**, **10**, and **11** have been prepared by Musker et al. using a general procedure for cyclization of dithiols.[10] Both the cyclic dimer[16] and tetramer[16] of 4,6-dimethyl-1,3-benzenedithiol have been prepared from the dithiol by oxidation with iodine. The preparation and spectral properties of 7 have been described by several groups.[11,12,17] Chan et al.[11] have prepared 7, **8**, and five methylated analogs by oxidation of the corresponding dithiols with NBS and pyridine in carbon tetrachloride. The reaction of 2,6-bis(bromomethyl)-pyridine with sodium sulfide gave 9 as a minor byproduct.[18] Oxidation of tetrafluoro-1,4-benzenedithiol with DMSO gave 13 in 95% yield.[19] Oxidation of dithiols with iodine using high dilution techniques generated the cyclic disulfides 2,[13] 3,[10] 4,[15] 5,[16] 6,[20] 10,[10] 11,[10] 12,[6] and 14.[16] In the current study we have used similar techniques to prepare cyclic disulfides from dithiols.

Results and Discussion

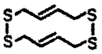
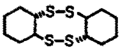
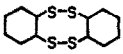
Synthesis and Characterization of Bis(disulfide) Dimers. We have prepared new cyclic bis(disulfides) of several dithiols by oxidation with iodine under high-dilution conditions, a procedure leading to kinetic products (Table I). Yields for high dilution reactions are typically poor (< 25%). The unexpected high yield in the reaction forming 15 (68%) probably reflects precipitation of this compound from solution as it forms. A similar high yield (95%) was obtained in the oxidation of 2,3,5,6-tetrafluoro-1,4-benzenedithiol with DMSO to compound 13.[19] Compound 15 is sparingly soluble in organic solvents (up to 10 mg/mL in benzene or toluene). The solid does not melt, but slowly polymerizes to a brittle



1 2 3 4 5 6 7 8 9 10 11 12 13 14

Figure 1. Structures of several previously reported cyclic disulfides.

Table I. Physical Properties of Cyclic Bis(disulfides).

Cmpd.	Structure	Yield	m.p. (°C)	Formula	Analysis			
						%C	%H	%S
15		68%	poly. >130	$C_{18}H_{18}S_6$	Found:	50.55	4.39	45.08
					Required:	50.67	4.25	45.08
16		10%	87-7	$C_8H_{12}S_4$	Found:	40.38	5.27	54.31
					Required:	40.64	5.12	54.24
4		21%	178-81	$C_{12}H_{20}S_4$	Found:	49.39	6.64	43.99
					Required:	49.27	6.89	43.84
17		15%	110-15 (poly.)	$C_{12}H_{20}S_4$	Found:	49.71	7.14	43.15
					Required:	49.27	6.89	43.84

yellow-orange solid when heated above 130 °C. Similar behavior is observed for dibenzo[1,2,5,6]tetrathiocin (2, R = H).[13] Neither electron impact nor chemical ionization mass spectrometry of 15 gave a parent ion. A molecular weight of 450 was obtained from melting point depression (Rast method), a value that is in satisfactory agreement with the molecular weight of 442 required for the dimer. The proton NMR spectrum of 15 consists of two singlet peaks, one for the benzylic protons occurring at δ = 3.3, and one for the aromatic proton at δ = 6.5. These peaks do not differ substantially in position from the corresponding peaks in the unoxidized trithiol. The simplicity of the spectrum suggests that there is largely unhindered interchange between conformers differing in the geometry of the cyclophane bridges. The analogous cyclophanes, 2,11,20-trithia[3.3.3](1,3,5)-cyclophane[21] and 4,11,24-trioxo-2,13,22-trithia[4.4.4](1,3,5)cyclophane[22] also show conformational flexibility.

1,2,7,8-Tetrathiacyclododeca-4,10-diene (16) was obtained on oxidation in only 10% yield. The dimer did not precipitate from solution as it was formed, and this solubility may account for the low yield. Melting point depression indicated a molecular weight of 250 (theory 236). The mass spectrum showed a small parent ion peak at m/e = 236. The proton NMR of 16 did not differ significantly from the spectrum of the corresponding dithiol.

Oxidation of cis-1,2-cyclohexanedithiol gave a yellow paste from which the desired cyclic bis(disulfide) dimer 17 was sublimed. The mass spectrum of 17 shows a large parent ion peak at m/e = 312. The proton NMR spectra of 17 and polymeric products obtained by iodine oxidation of a concentrated solution of the dithiol differ substantially from one another. NMR spectroscopy was used routinely to differentiate dimeric and polymeric species, both in this study and in related studies of thiol-disulfide interchange.[1]

Polymerization of 17 occurs in the solid state as the dimer is heated. The ^{1}H NMR of a sample of dimer that had been heated above its melting point showed peaks due to both dimer and polymer.[23]

Oxidation of trans-1,2-cyclohexanedithiol was carried out in a similar manner to give 4. The mass spectrum of 4 is very similar to that of 17. The proton NMR spectra of 4 and polymeric disulfide derived from the same dithiol are quite distinct. The spectrum of the dimer is complicated due to the existence of two diastereomers.

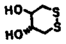
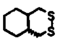
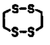
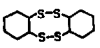
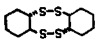
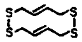
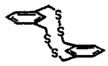
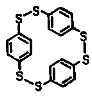
Stability of Cyclic Disulfides toward Polymerization. The stability of a cyclic disulfide in neat form is dependent upon its structure and purity. Lipoic acid is relatively stable in the solid state.[30] If, however, the disulfide is heated above its melting point, polymerization occurs readily.[24] For the disulfides of C_5-C_{12} n-alkyl α,ω-dithiols, both the six- and seven-membered ring compounds are reported to be quite stable in neat form.[25] A conflicting study on the same series of disulfides reports that only seven-, nine- and eleven-membered rings are stable indefinitely in neat form.[26] A study of the properties of 5-15-membered ring cyclic monomeric disulfides reports only 3,3,5,5-tetramethyl-1,2-dithiocyclopentane and 1,2-dithiane to be stable to polymerization.[27] These differing reports may reflect differences in purities of the disulfides. 1-Oxa-4,5-dithiacycloheptane polymerizes in neat form, or in the presence of a catalyst[26] (ΔH polymerization = 1.9 kcal/mol at 27 °C[28]), while a very pure, dry sample of the same disulfide was reported to remain unpolymerized after standing for five years at room temperature.[29]

Reports of stability of individual cyclic disulfides include: i) compounds that polymerize on standing, such as 3,3-dimethyl-1,2-dithiolane,[25,27] 3-hydroxy-1,2-dithiolane (which polymerizes in a few days),[31] and N-phenyl-4-oxo-5-aza-1,2-dithiacyclohexane ($t_{1/2}$ = 12 h)[20]; ii) compounds that polymerize when heated, such as dibenzo-1,2,5,6-tetrathiocin, a substance reported as stable for 21 months at 25 °C, but that polymerizes upon heating (the MW doubles in 16 h in refluxing benzene)[13]; iii) compounds that polymerize in neat form when a catalyst is added, such as cis-1,2-dithiacyclohex-4-ene[27] and 1-oxa-4,5-dithiacycloheptane.[26,28,29]

We wished to determine if the stabilities of neat cyclic disulfides correlated with the tendency of the corresponding dithiols to cyclize under equilibrating conditions. Table II presents data for compounds we have prepared and examined. The table summarizes physical properties of disulfides and information regarding conditions of polymerization and characteristics of polymeric products.

Stability to polymerization was determined by exposing disulfides to a catalytic amount of base. Thermodynamically stable cyclic disulfides remain intact under these conditions. The general procedure for these experiments was to make up two tubes containing the disulfide, one with no base and one with ca. 1-2% (w:w) added sodium methanethiolate. The tubes were heated to a temperature slightly above the melting point of the disulfide and any changes noted. In most cases the liquid cyclic disulfide became opaque or solidified as polymer formed. Bis(disulfides) 4 and 17 remained liquids during this procedure; these liquids cooled to sticky solids that showed ^{1}H NMR spectra indistinguishable from polymeric material. Bis(disulfide) 3 polymerized to a solid at 70 °C, but melted again if the temperature was raised to >150 °C. A melting range of 150 to 154 °C for a linear polymeric form of 1,2-ethanedithiol has been reported by several investigators.[32]

Table II. Stability of Cyclic Disulfides to Polymerization When Melted in the Presence of $NaSCH_3$.

Cmpd	Structure	m.p. (°C)	Oil Bath Temp (°C)	Time[a] (min)	Behavior as a Liquid Melt with NaSMe	Ring Size
18		130-2	140	>480	no change (by ^1H NMR)	6
19		56-8	70	>480	no change (by ^1H NMR)	6
20		32-3	70	>480	no change (by ^1H NMR)	6
21		liquid	70	>180	turns to a sticky, cloudy white solid	7
22		viscous liquid	70	<15	solidifies to a cloudy white solid	8
3		62-4	70	<15	solidifies to a yellow solid; remelts if the temp is increased to >160 °C	8
4		178-181	185	<15	remains a liquid at elevated temp, complete polymerization has occurred (by ^1H NMR)	8
17		110-115 (poly.)	185	<15		8
16		84-87	90	<5	turns to a yellow insoluble liquid	12
7		173-176	180	<5	turns to a yellow insoluble liquid	14
15		---	---	--	does not melt; polymerizes to a yellow insoluble solid when heated to >130 °C with no base added	14
12		150-153	180	<5	turns to a yellow insoluble solid	18

[a] Length of time for which the compound remains in monomeric form when melted in the presence of $NaSCH_3$.

The ^1H NMR spectrum of 7 exhibits a characteristic peak at 6.35 ppm. This peak corresponds to shielded protons at the C2 position of the aromatic ring.[12] The peak disappears when 7 is melted in the presence of NaSMe. Using the characteristic peak at 6.35 ppm, it is possible to determine if 7 is formed under conditions in which thiol-disulfide interchange generates an equilibrium mixture of species. This peak does not appear in the spectra of the equilibrated species, which are therefore assigned oligomeric structures. It is also not observed when 1,3-bis(mercaptomethyl)benzene is equilibrated against oxidized 2-mercaptoethanol (ME^{ox}). The equilibration can also be carried out in the opposite direction; the 6.35 ppm peak in a 1 mM solution of the dimer slowly disappears when the disulfide is equilibrated against 2 mM mercaptoethanol.

Conclusions

We conclude that the only class of simple cyclic disulfides that is thermodynamically stable with respect to polymer in the melt or as concentrated solutions is the 1,2-dithianes (e.g. compounds **18**, **19**, and **20**). A number of compounds are relatively stable *kinetically* in the absence of a catalyst for thiol-disulfide interchange, but this stability disappears in the presence of an effective catalyst. These results reinforce conclusions drawn from studies of redox potentials concerning cyclic disulfide-containing systems.[1,2]

These studies are also useful in establishing the identity of the cyclic disulfides for comparison with compounds, and mixtures of compounds, formed under equilibrating conditions. In thiol-disulfide interchange studies, we have found that a number of five-, six-, seven-, and eight-membered cyclic disulfides and bis(disulfides) *are* stable with respect to polymer in more dilute solutions (~10 mM).[1] We have not yet carried out a detailed balance in energies for these substances. We *observe* polymerization (usually with precipitation of polymer) in concentrated solutions (~10 M), and apparently stable solutions of cyclic disulfides and bis(disulfides) at concentrations (10 mM) more dilute by a factor of approximately 10^3. The change in ΔG due to entropy of dilution is readily estimated to be $RT\Delta S \simeq 5.5$ kcal/mol. There may, in addition, be contributions to ΔG due to phase changes (precipitation) or to other processes.

Experimental

General. All reactions and measurements were carried out under an atmosphere of nitrogen or argon. 1,2-Dithiane was obtained from Columbia Organic Chemicals. Deuterated solvents and other chemicals were obtained from Aldrich Chemical Co. Commercially available thiols were recrystallized or distilled under nitrogen before use. Tetrahydrofuran (THF) was distilled from disodium benzophenone dianion before use. Rast molecular weights were determined using benzophenone as the solid solvent. Melting points are uncorrected. Mass spectra were obtained using a Kratos MS-50 spectrometer. Elemental analyses were performed by Spang Laboratories, Eagle Harbor, MI or Atlantic Microlab, Inc., Atlanta, GA.

Preparations of Cyclic Disulfides

2,3,12,13,22,23-hexathia[4.4.4](1,3,5)cyclophane (15). 1,3,5-Tris(mercaptomethyl)benzene[1] (1 g, 4.7 mmol) in ethanol (400 mL) and iodine (1.76 g, 6.93 mmol) in ethanol (400 mL) were added simultaneously, via constant addition rate dropping funnels, to rapidly stirred ethanol (600 mL) over a three-hour period. The rates of addition of thiol and iodine were adjusted so that the reaction mixture remained slightly yellow from a small excess of iodine. The white precipitate that formed was collected by filtration and washed with ethanol (3 x 30 mL). The product was recrystallized by dissolving it in benzene at room temperature and slowly cooling the solution to 0 °C to give 0.68 g (68%) of **15** as a fine white powder. The compound polymerizes to an insoluble yellow-orange solid if it is dissolved in hot benzene. Compound **15** does not melt when heated (up to 300 °C), but it begins to polymerize to an orange solid at >130 °C: ^{1}H NMR (d_6-benzene) δ 6.5 (s, 3 H), 3.3 (s, 6H); Rast mol wt[33] 450 ± 20 (mol wt calcd for $C_{18}H_{18}S_6$ = 442).

1,2,7,8-tetrathiacyclododeca-4,10-diene (16) was prepared in analogy to 15. *Trans*-2-butene-1,4-dithiol[1] (0.32 g) gave 34 mg (10%) of **16** as a white solid: mp 84-87 °C; ^{1}H NMR ($CDCl_3$) δ 5.6 (m, 2H), 3.3 (dd, 4H); Rast mol wt[33] = 250 ± 20 (mol wt calcd for $C_8H_{12}S_4$ = 236); mass spectrum (70 eV), *m/e* (rel intensity) 236 (1), 150 (14), 119 (11), 118 (46), 117 (10), 103 (28), 87 (25), 86 (24), 85 (94), 84 (29).

***Trans*-dodecahydro-dibenzo[1.2.5.6]tetrathiocin (4)** was prepared using a procedure similar to that for the synthesis of 15. *Trans*-1,2-cyclohexane dithiol[1] (5 g, 0.34 mol) in chloroform (450 mL) and iodine (8.55 g, 0.34 mol) in chloroform (450 mL) were added simultaneously, via constant addition rate dropping funnels, to a rapidly stirred solution of triethylamine (6.8 g, 0.068 mol) in chloroform (750 mL) over a 3-h period. A small amount of sodium bisulfite was added to the solution at the completion of the reactions to destroy the slight excess of iodine that remained. The solution was washed with 0.1 M hydrochloric acid (2 x 200 mL) and water (3 x 200 mL), dried ($MgSO_4$), and the solvent removed at reduced pressure to give a sticky yellow paste (5 g). The paste (1.4 g) was sublimed (130-145 °C at 0.05-0.1 torr) to give 0.3 g (21%) of a white solid. Recrystallization from hot hexanes afforded **4** as fine white needles: mp 178-181 °C (lit.[15] mp 191.5-192 °C); ^{1}H NMR ($CDCL_3$) δ 3.5 (m, 1H), 3.0 (m, 2H), 2.3 (m, 2H), 2.1 (m, 3H), 1.7 (m, 4H), 1.1-1.5 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 58.5, 57.4, 54.2, 38.1, 36.4, 35.2, 26.7, 26.6, 26.1; mass spectrum (70 eV), *m/e* (rel intensity) 294 (9), 292 (45), 178 (87), 146 (4), 114 (19), 113 (21), 81 (100).

***Trans*-1,2-cyclohexanedithiol-disulfide polymer** remained behind when the dimeric species was sublimed: ^{1}H NMR ($CDCl_3$) δ 2.9 (m, 2H), 2.3 (m, 2H), 1.7 (m, 2H), 1.55 (m, 2H), 1.3 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 53.4-53.1, 31.8-31.4, 24.6-24.4.

***Cis*-dodecahydro-dibenzo[1.2.5.6]tetrathiocin (17)** was prepared from *cis*-1,2-cyclohexanedithiol[1] in 15% yield in analogy to 15. Sublimation (125-135 °C at 0.50-0.1 torr) afforded the product as a white solid: mp 105-110 °C; ^{1}H NMR ($CDCl_3$) δ 3.6 (t, 1H), 3.5 (t, 1H), 1.2-1.9 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 62.1, 44.8, 30.0, 29.1, 24.1; mass spectrum (70 eV), *m/e* (rel intensity) 292 (22), 178 (49), 146 (5), 114 (20), 113 (9), 81 (100).

***Cis*-1,2-cyclohexanedithiol-disulfide polymer** remained behind when the dimeric species was sublimed: ^{1}H NMR ($CDCl_3$) δ 3.3 (m, 2H), 1.2-2.0 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 55.7-55.3, 30.9-29.8, 23.9-22.8.

1,2,5,6-Tetrathiacyclooctane (3) was prepared in 41% yield by iodine oxidation of 1,2-ethanedithiol according to the procedure of Goodrow, Olmstead and Musker,[10] mp 62-64 °C (lit.[10] mp 62-64 °C).

2,3,12,13-Tetrathia[4.4]metacyclophane (7) was prepared in analogy to 15. Recrystallization from hot benzene gave 7 in 63% yield as small white nodules: mp 173-176 °C (lit.[17] 170-171 °C).

Para-tri(phenylenedisulfide) (12) was prepared in 25% yield by iodine oxidation of 1,4-benzenedithiol according to the procedure of Wong and Marvel,[6] mp 149-153 °C (lit.[6] mp 150-153 °C).

***Trans*-2,3-dithiadecalin (19)** was prepared from *trans*-1,2-bis(mercaptomethyl)cyclohexane[1] using a general procedure for the iodine oxidation of α,ω-dithiols to the corresponding cyclic monomeric disulfides.[34] Recrystallization from 3:1 hexane/methanol provided **19** as a white solid: mp 56-58 °C (lit. mp[35] 56.5-57.5 °C).

1,2-Dithiacycloheptane (21) was prepared from 1,5-pentane-dithiol in 88% yield using the same procedure as in the synthesis of **19**. Kugelrohr distillation (45-50 °C at 0.5 torr, lit.[36] bp 55-60 °C at 1.7 torr) afforded the product as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.8 (t, 4H), 2.0 (quintet, 4H), 1.7 (quintet, 2H).

1,2-Dithiacyclooctane (22) was prepared from 1,6-hexane-dithiol in 72% yield using the same general procedure as in the synthesis of **19**. Kugelrohr distillation (60-64 °C at 1 torr, lit.[27] bp 65.5 °C at 2 torr) afforded the product as a colorless viscous liquid: ^{1}H NMR ($CDCl_3$) δ 2.6 (t, 4H), 1.7 (quintet, 4H), 1.4 (m, 4H).

Determination of the Stability of Cyclic Disulfides and Bis(disulfides) toward Polymerization. In a typical experiment, two samples of cyclic disulfide (15-20 mg) were weighed into 1-mL test tubes. To one of the tubes was added 0.2 M sodium methanethiolate in methanol (20 μL, ca. 1-2% w:w of sodium methanethiolate relative to cyclic disulfide). The tubes were heated in an oil bath and any changes noted. Results of these experiments are summarized in Table II.

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